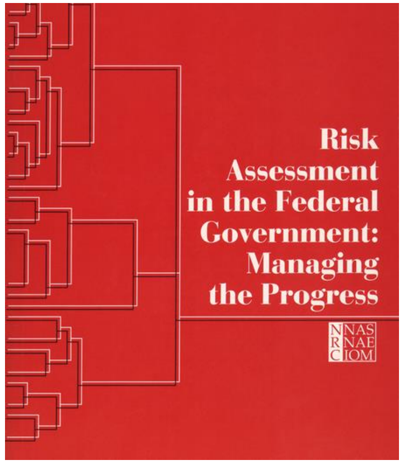
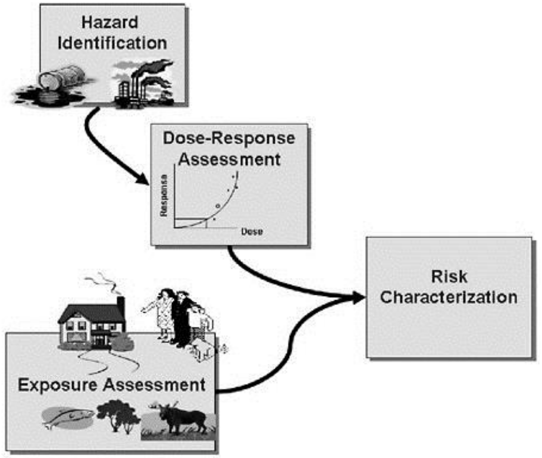
# The Future of Human Health Assessments:

## *Using New Methodologies for Better Understanding of the Health Impacts of Petroleum Substances*

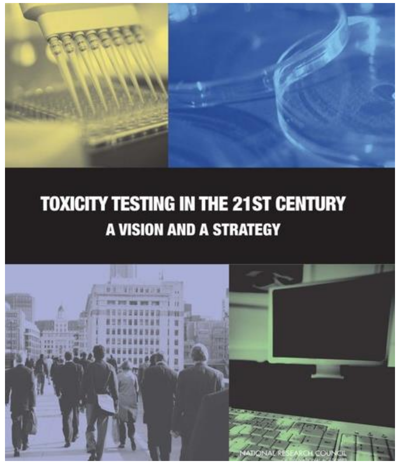
**Ivan Rusyn, M.D., Ph.D.**
Professor of Veterinary Integrative Biosciences
Chair, Interdisciplinary Faculty of Toxicology
Texas A&M University
United States of America

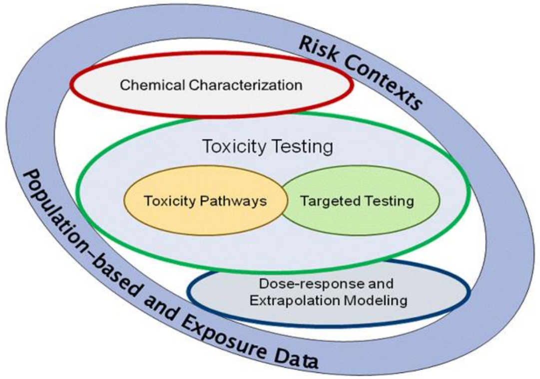
1983



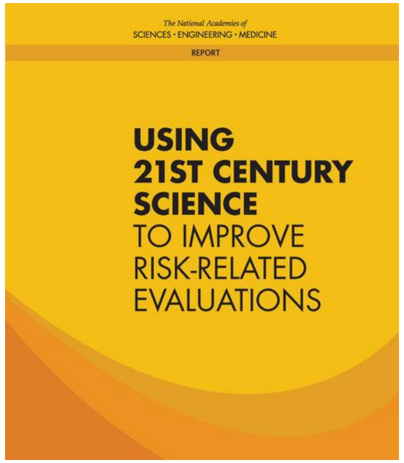



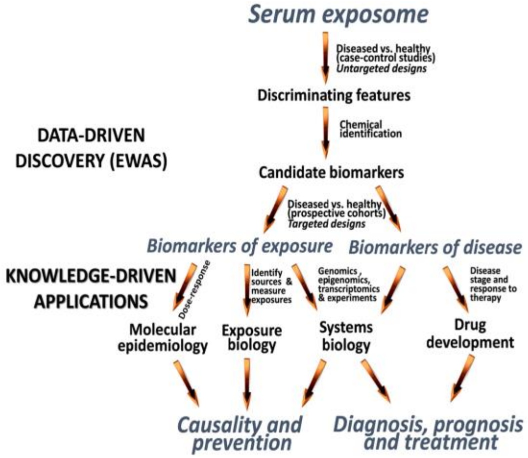

2007



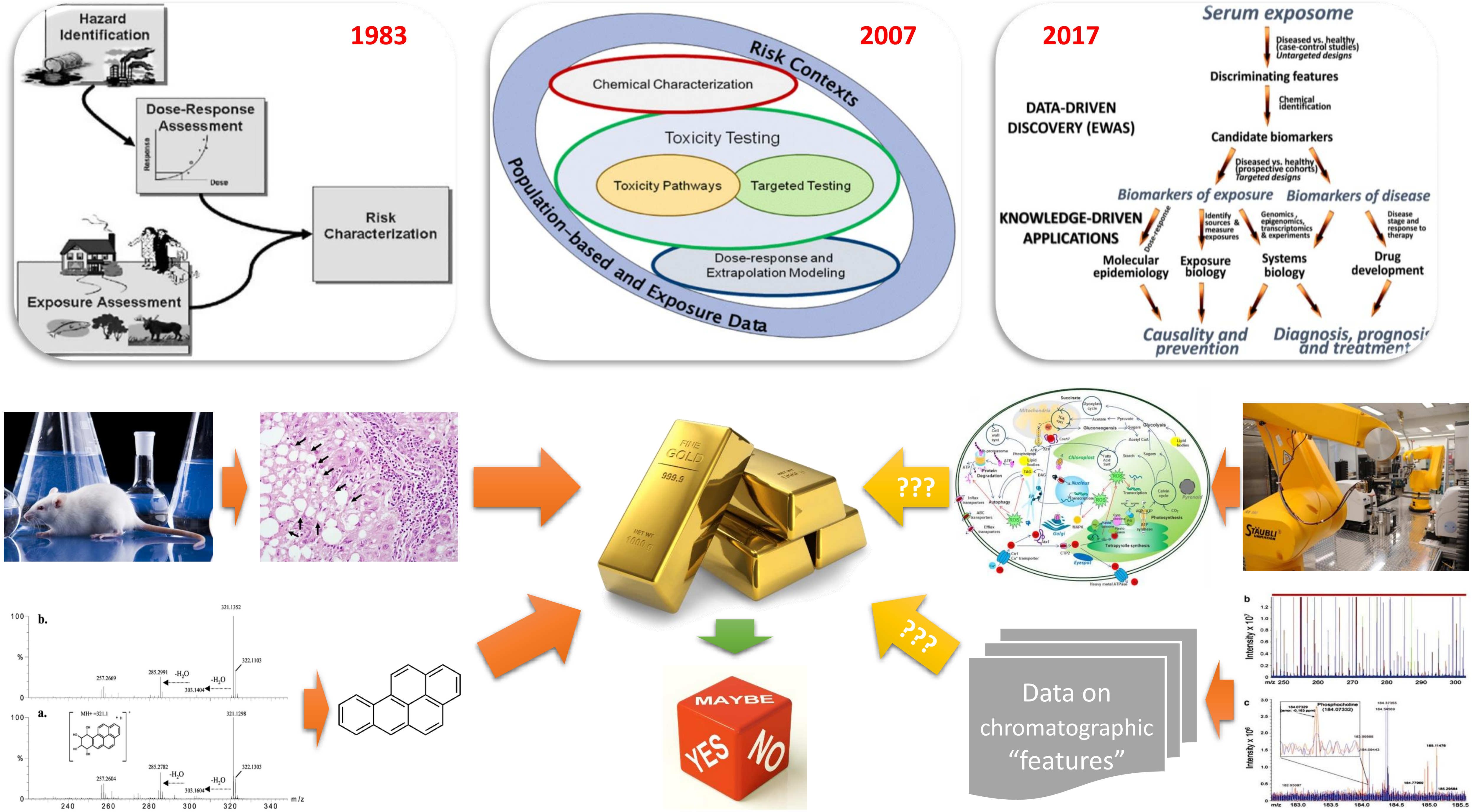




2017




Images of BMW 3 series vehicles are from edmunds.com; Other images are from nas.edu



1983
Hazard Identification
Dose-Response Assessment
Response
Dose
Risk Characterization
Exposure Assessment
2007
Risk Contexts
Chemical Characterization
Toxicity Testing
Toxicity Pathways
Targeted Testing
Dose-response and Extrapolation Modeling
Population-based and Exposure Data
2017
Serum exposome
Diseased vs. healthy (case-control studies) Untargeted designs
Discriminating features
Chemical identification
Candidate biomarkers
Diseased vs. healthy (prospective cohorts) Targeted designs
DATA-DRIVEN DISCOVERY (EWAS)
Biomarkers of exposure
Biomarkers of disease
KNOWLEDGE-DRIVEN APPLICATIONS
Dose-response
Identify sources & measure exposures
Genomics, epigenomics, transcriptomics & experiments
Disease stage and response to therapy
Molecular epidemiology
Exposure biology
Systems biology
Drug development
Causality and prevention
Diagnosis, prognosis and treatment
???
???
MAYBE
YES
NO
Data on chromatographic “features”

# Drivers for Change

- Ethics

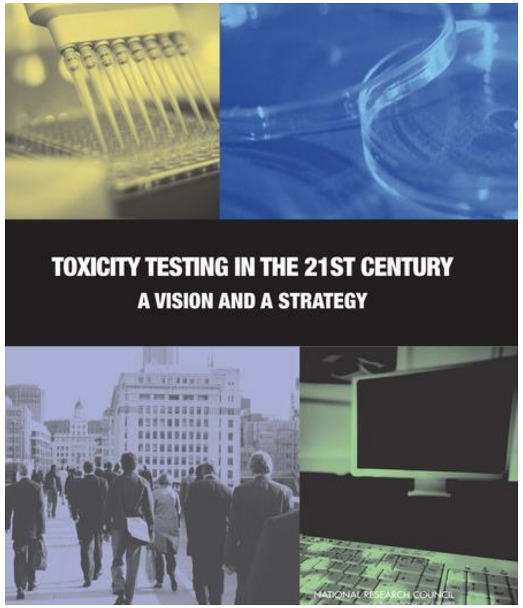
- Efficiency

- Public Health (Human Relevance)

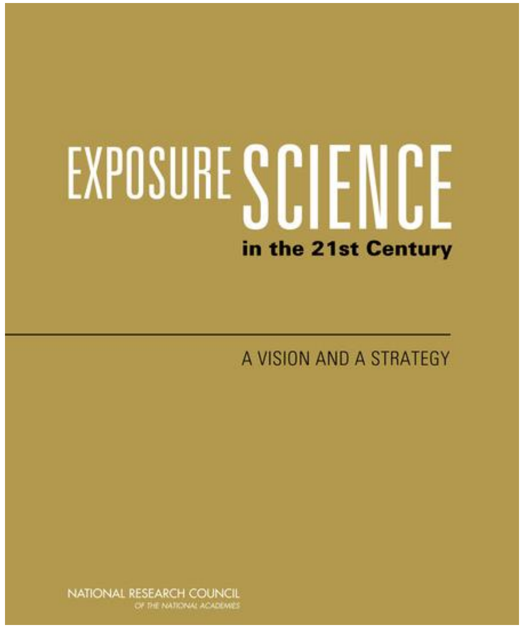
- Legislation

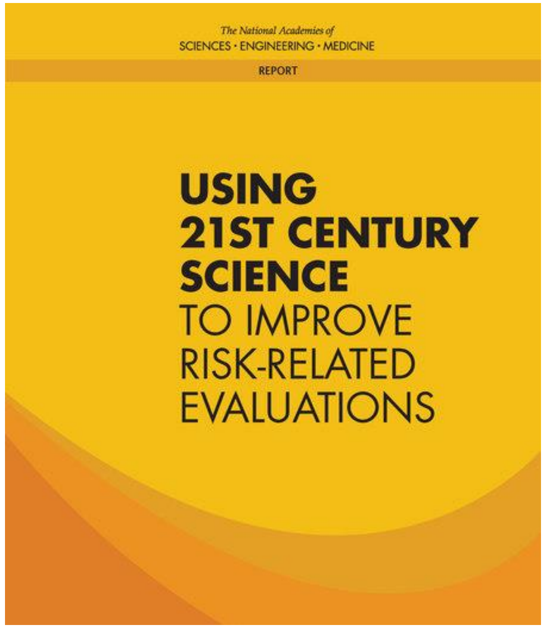
Slide courtesy of W. Casey (NIEHS-NTP)

***Toxicity Testing in the 21st Century: A Vision and a Strategy*** was published in 2007 and envisioned a future in which toxicology relied primarily on high-throughput *in vitro* assays and computational models based on human biology to evaluate potential adverse effects of chemical exposure.




***Exposure Science in the 21st Century: A Vision and a Strategy*** was published in 2012 and provided a vision that was hoped to inspire transformational changes in the breadth and depth of exposure assessment that would improve integration with and responsiveness to toxicology and epidemiology






## *Committee Charge:*

- to provide recommendations on integrating new scientific approaches into risk-based evaluations

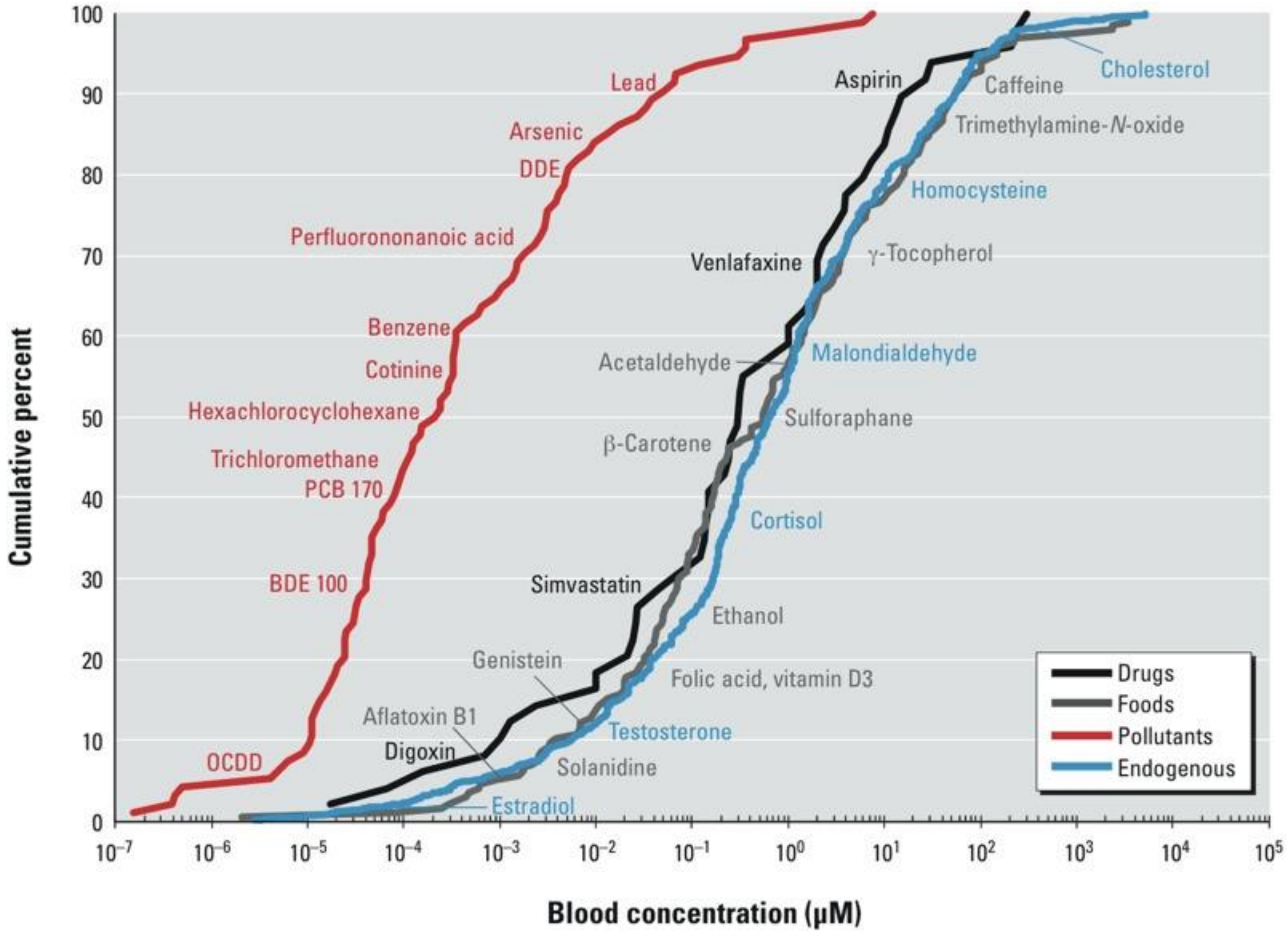
## *Committee Sponsors:*

- US Environmental Protection Agency
- US Food and Drug Administration
- National Institutes of Health (NIEHS and NCATS)

| *TOXICOLOGY* | *EPIDEMIOLOGY* | *EXPOSURE* | *STATISTICS* |
|---|---|---|---|
| George Daston | Jonathan Samet | Melvin Andersen | David Dunson |
| Nigel Greene | Esteban Burchard | Jon Arnot | Fred Wright |
| Heather Patisaul | Beate Ritz | Justin Teeguarden | |
| Kristi Pullen | Paolo Vineis | | |
| Ivan Rusyn | Michelle Williams | | |
| Robert Tanguay | | | |
| James Tiedje | | | |
| Lauren Zeise | | | |

*"Exposure scientists, toxicologists, epidemio-logists, and other [subject matter experts] need to collaborate closely to ensure that the full potential of 21st century science is realized."*

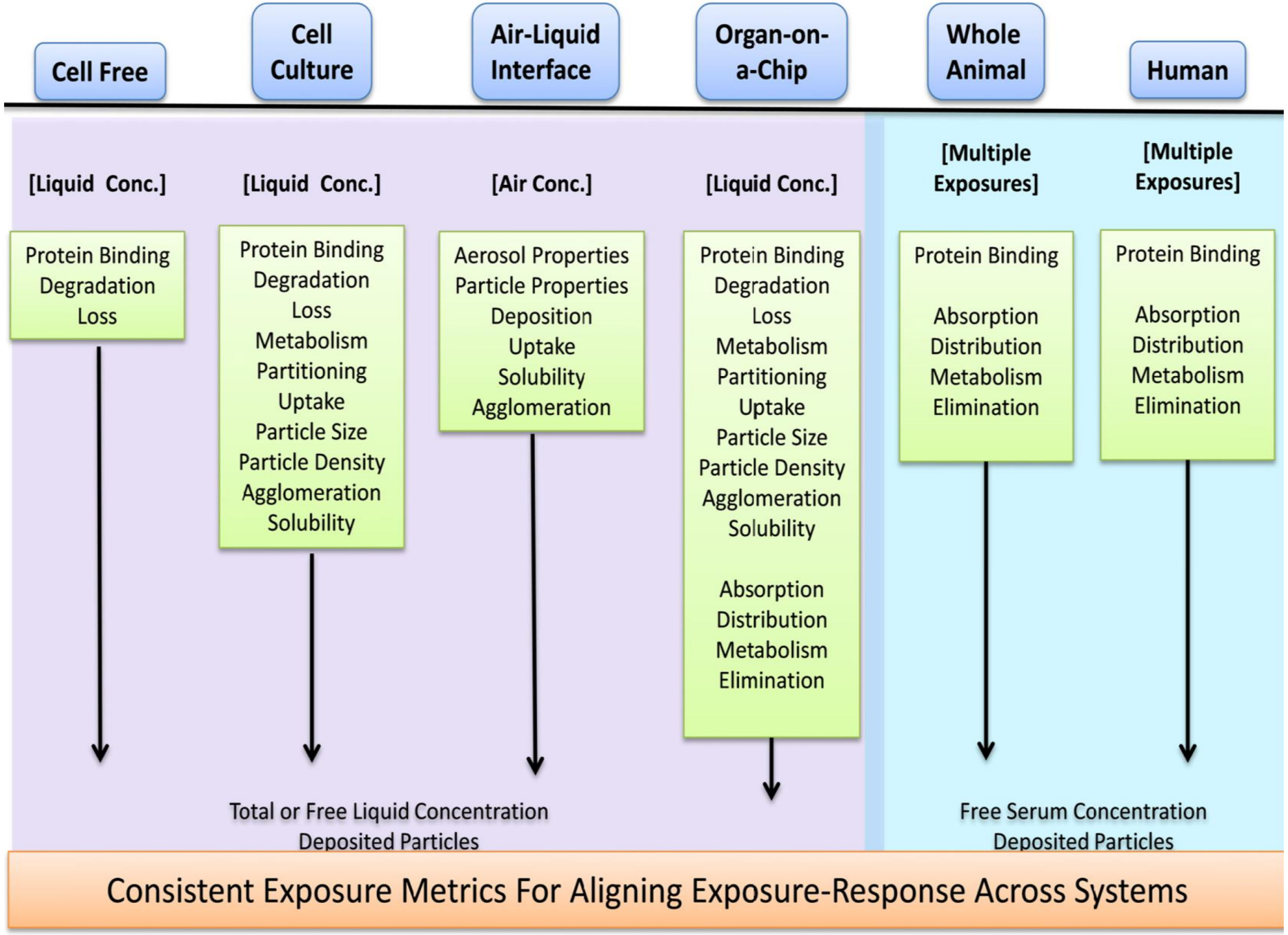
# Advances in Exposure Science




- Remote sensing, personal sensors, and other sampling techniques
- Computational exposure tools
- Targeted and non-targeted analyses
- –Omics technologies
- Novel exposure matrices for life-span research
- Physiologically based pharmacokinetic models

Environ Health Perspect. 2014 Aug; 122(8): 769–774.

# Future Applications for Exposure Sciences



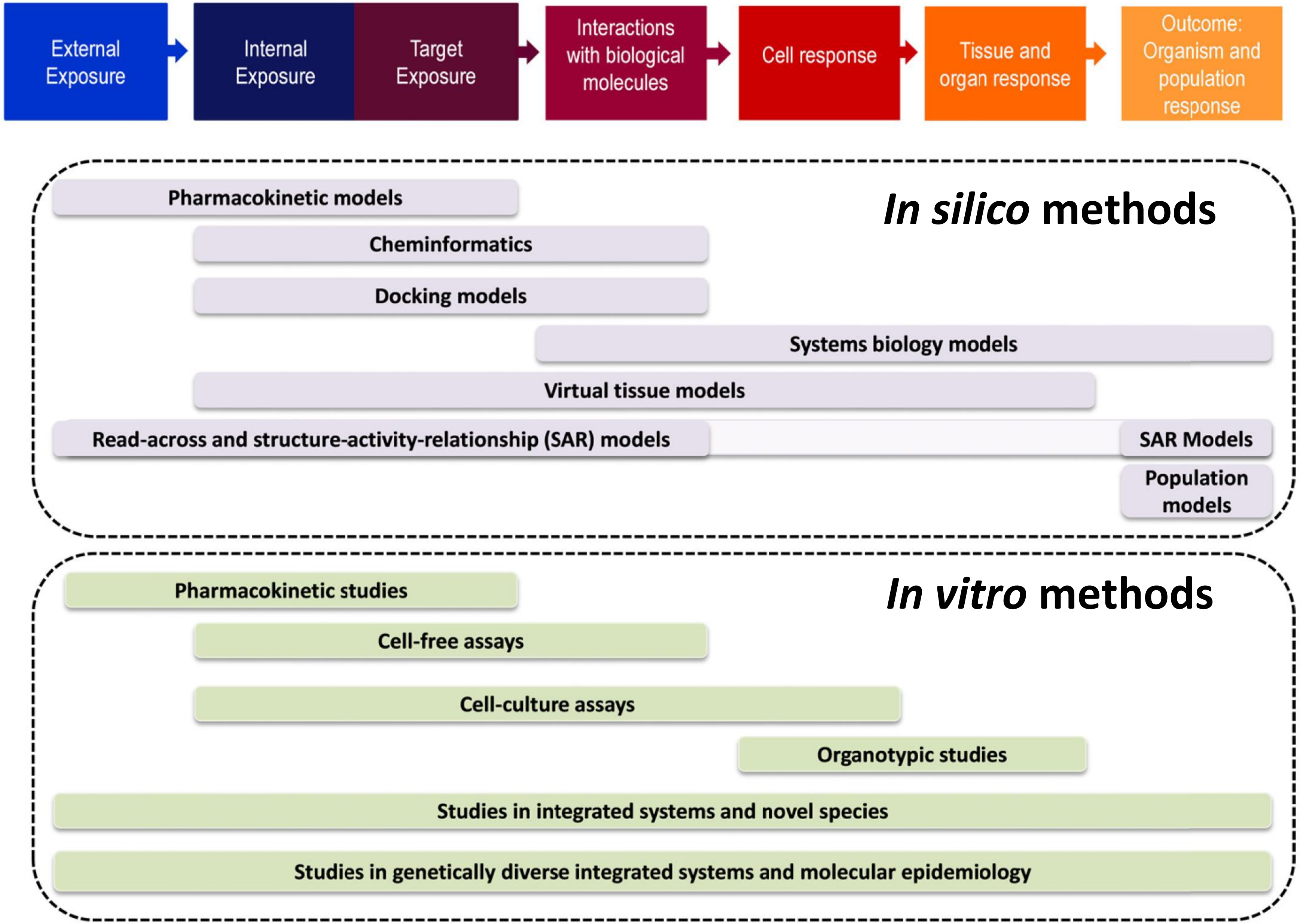

- Aligning exposures between test systems and humans
- Improving exposure assessment for epidemiological studies
- Exposure-based screening and priority-setting
- Identifying new chemical exposures for toxicity testing
- Predicting exposure to support registration and use of new chemicals
- Identifying, evaluating, and mitigating sources of exposure
- Assessing cumulative exposure and exposure to mixtures

# Advances in Toxicology

"Adverse Outcome Pathway"

*vs*

"Mechanism of Toxicity"

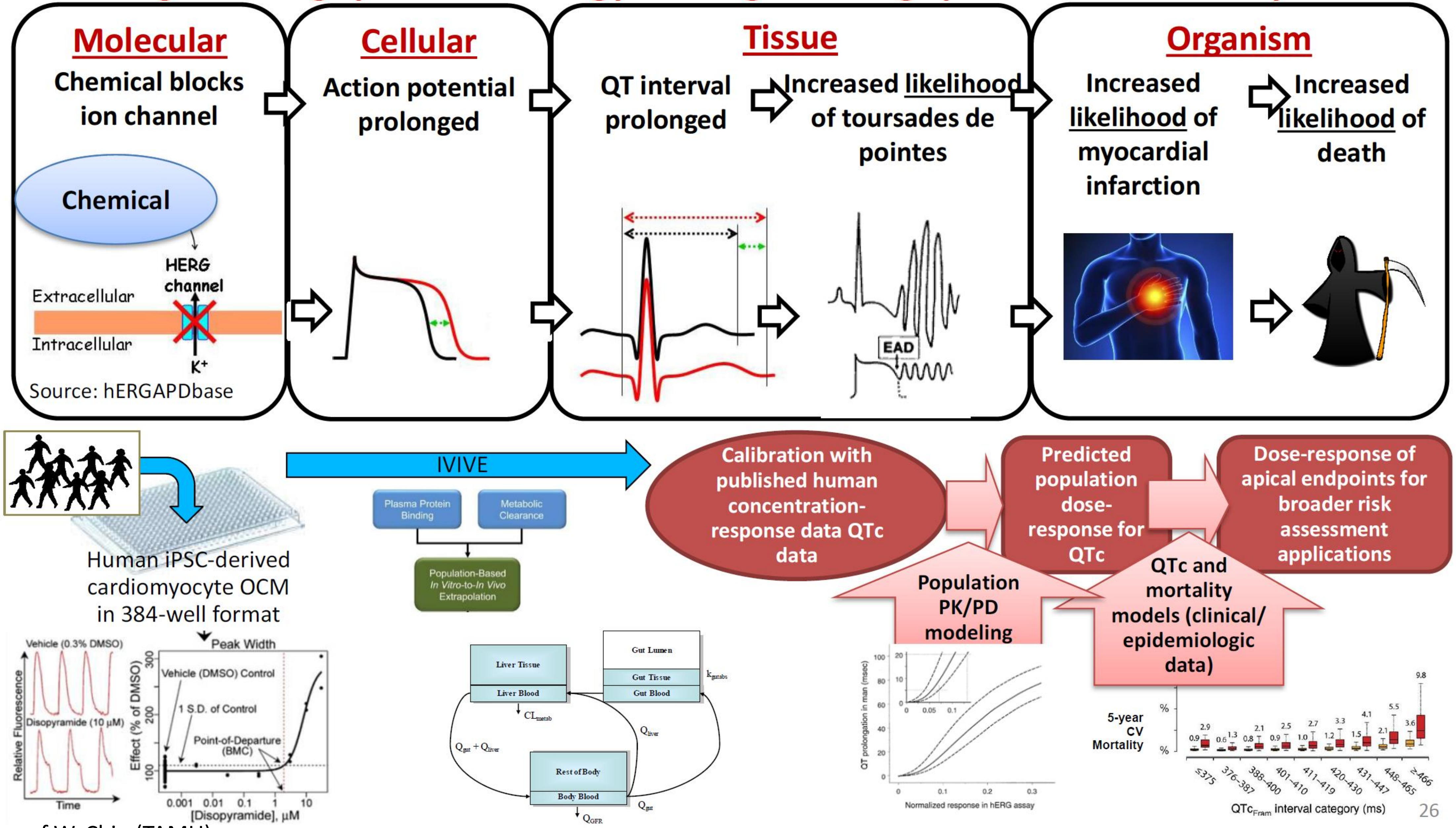



Technology advances *[largely spurred by the human genome project]* that enable more precise and higher throughput assays and methods

# Advances in Toxicology

- ***Probing interactions with biological molecules***. *In vitro* assays can probe chemical interactions with cells/molecules in low-, medium-, and high-throughput formats.
- ***Detecting cellular responses***. Cell cultures can evaluate a number of cellular processes and responses that may be indicative on *in vivo* effects.
- ***Investigating effects at higher levels of biological organization***. Advances in engineered 3-D models of tissues, which recapitulate at least some of the physiological responses that the tissue or organ exhibits *in vivo*.
- ***Predicting organism and population response***. Genetically diverse rodent strains and human cell lines can be used to address questions related to inter-individual sensitivity to toxicants.

# New Tox Assays and Adverse Outcome Pathway: Cardiotoxicity




Slide courtesy of W. Chiu (TAMU)

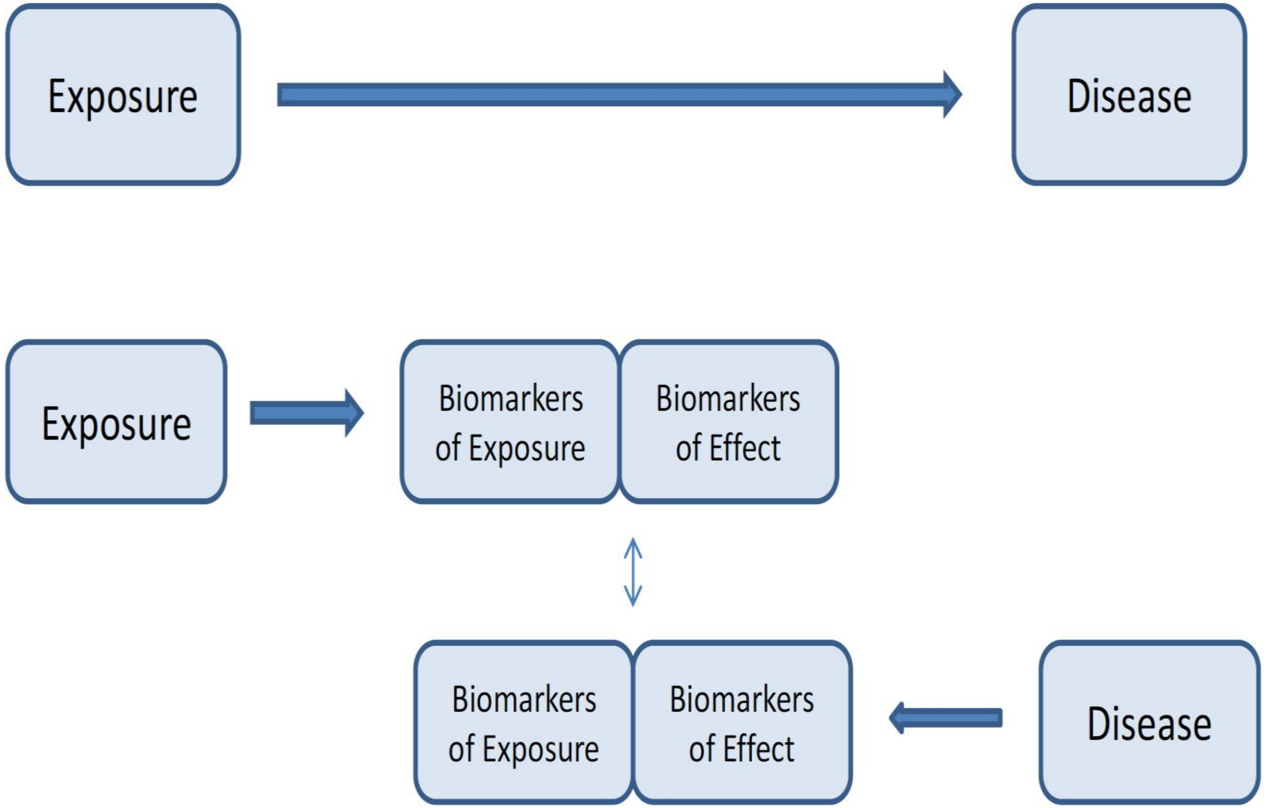
# Challenges with New Toxicology Methods

- Accounting for metabolic capacity in assays.
- Understanding and addressing other limitations of cell systems.
- Addressing biological coverage.
- Applications is decision-making beyond prioritization for *in vivo* animal tests.

| Read-Across Scenarios: Characteristics of Anchor and Data-Sparse (DS) Chemicals | Inferring Hazard and Dose-Response Relationships for Data-Sparse (DS) Chemicals from Anchor Chemicals | Examples |
| --- | --- | --- |
| Anchor and DS chemicals are all metabolized to same toxic metabolites. | Hazard: Assume same<br>Dose-Response: Adjust for pk in metabolite formation | Dyes that metabolize to dimethoxybenzidine |
| Anchor and DS chemicals have highly similar metabolic activation. Anchor chemicals show same hazards. | Hazard: Assume same<br>Dose-Response: Adjust for pk and bioactivity of metabolites | Various glycol ethers metabolized to alkoxyacids, sets of nitrosoamines |
| Anchor and DS chemicals have highly similar patterns of upstream biological effect.<br>Anchor chemicals show same hazards. | Hazard: Assume same<br>Dose-Response: Adjust for pk and differences in levels of bioactivity | Dioxin-like compounds (dioxins, furans, co-planar PCBs), PBDEs |
| Anchor and DS chemicals have similar patterns of biological activity.<br>Anchor chemicals show similar and related but not identical hazards | Hazard: Assume hazard based on upstream testing<br>Dose-Response: Adjust for pk and bioactivity after testing | Sets of *ortho*-Phthalates, PAHs |

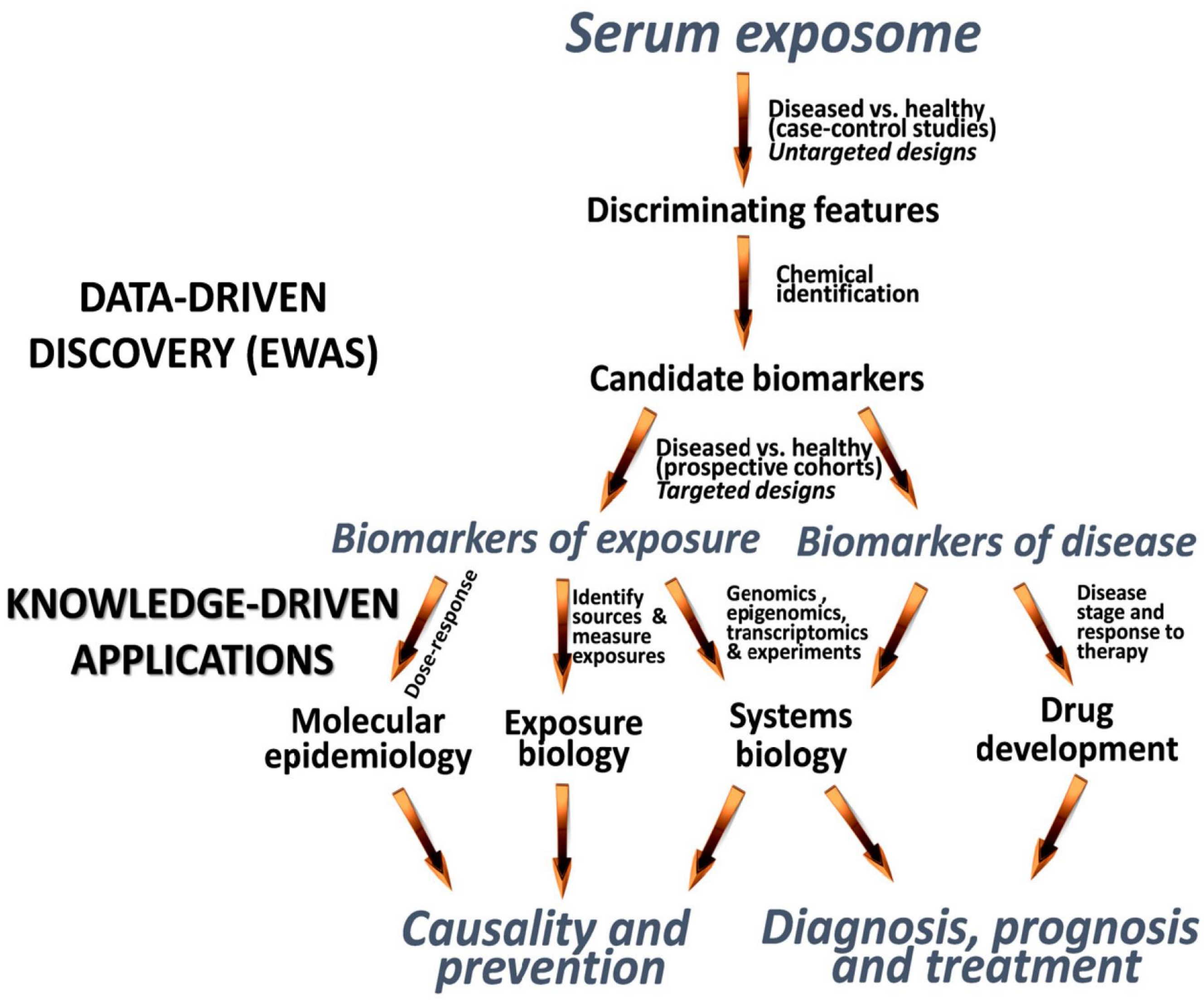
# Advances in Epidemiology

- Expansion of the interdisciplinary nature of the field.
- Increasing complexity of scientific inquiry.
- Emergence of new data sources and technologies for data generation.
- Advances in exposure characterization.
- Increasing demands to integrate new knowledge from basic, clinical, and population sciences.



# Challenges in Epidemiology

- -Omics assays can generate extremely large datasets.
- Databases, robust statistical techniques, and standard approaches to describe data are needed.
- Movement from fixed, specific cohorts to large cohorts enrolled from healthcare organizations that incorporate biospecimen banks and use healthcare records.



# Using 21st Century Science in Decision-Making: Defining the Areas of "Fit for Purpose"

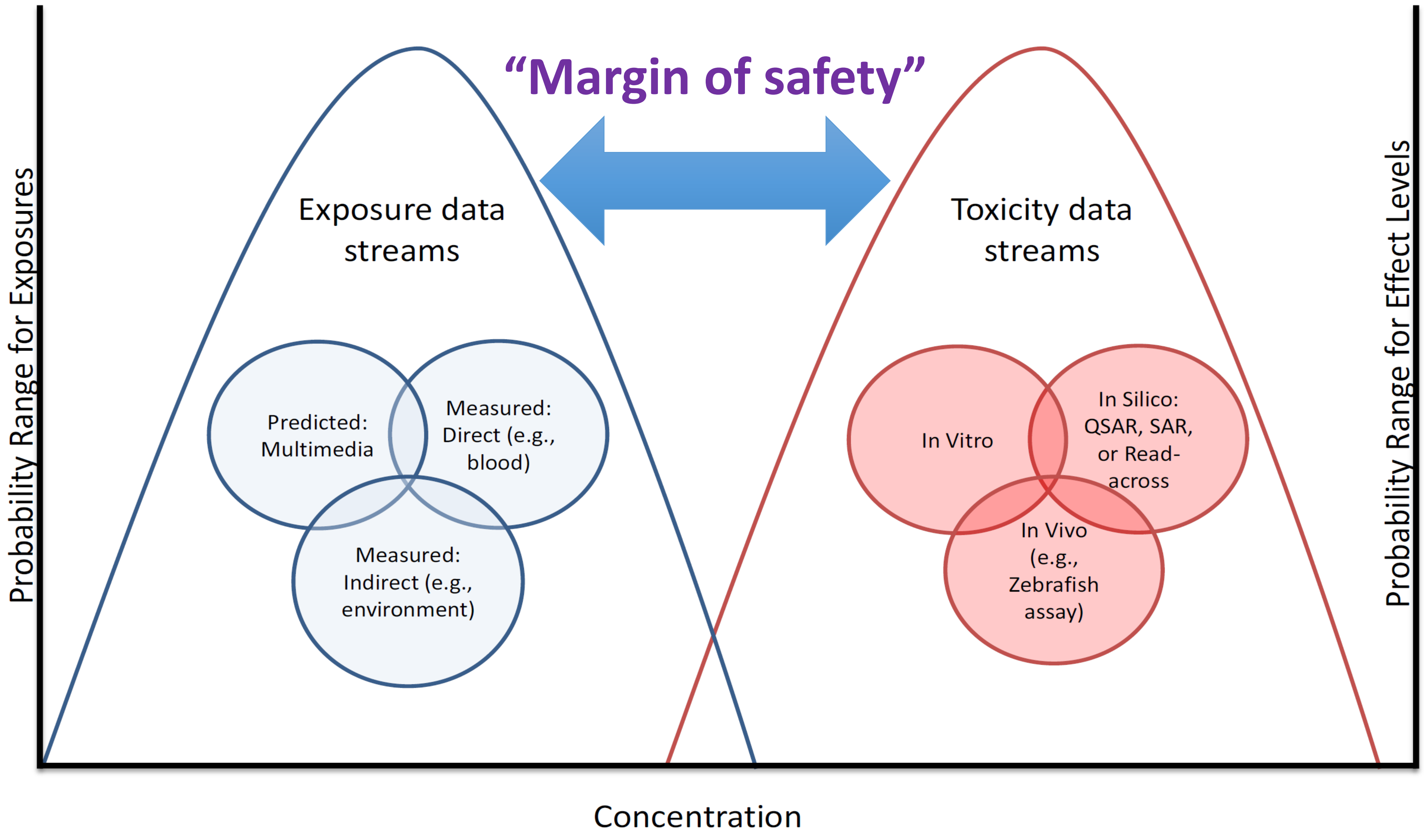
**Priority-setting:** Can be based on hazard, exposure, or risk.

**Assessment of mono-constituent chemicals:** Can be included in traditional chemical hazard and dose-response assessments of various regulated substances, such as pesticides, drugs, and food additives.

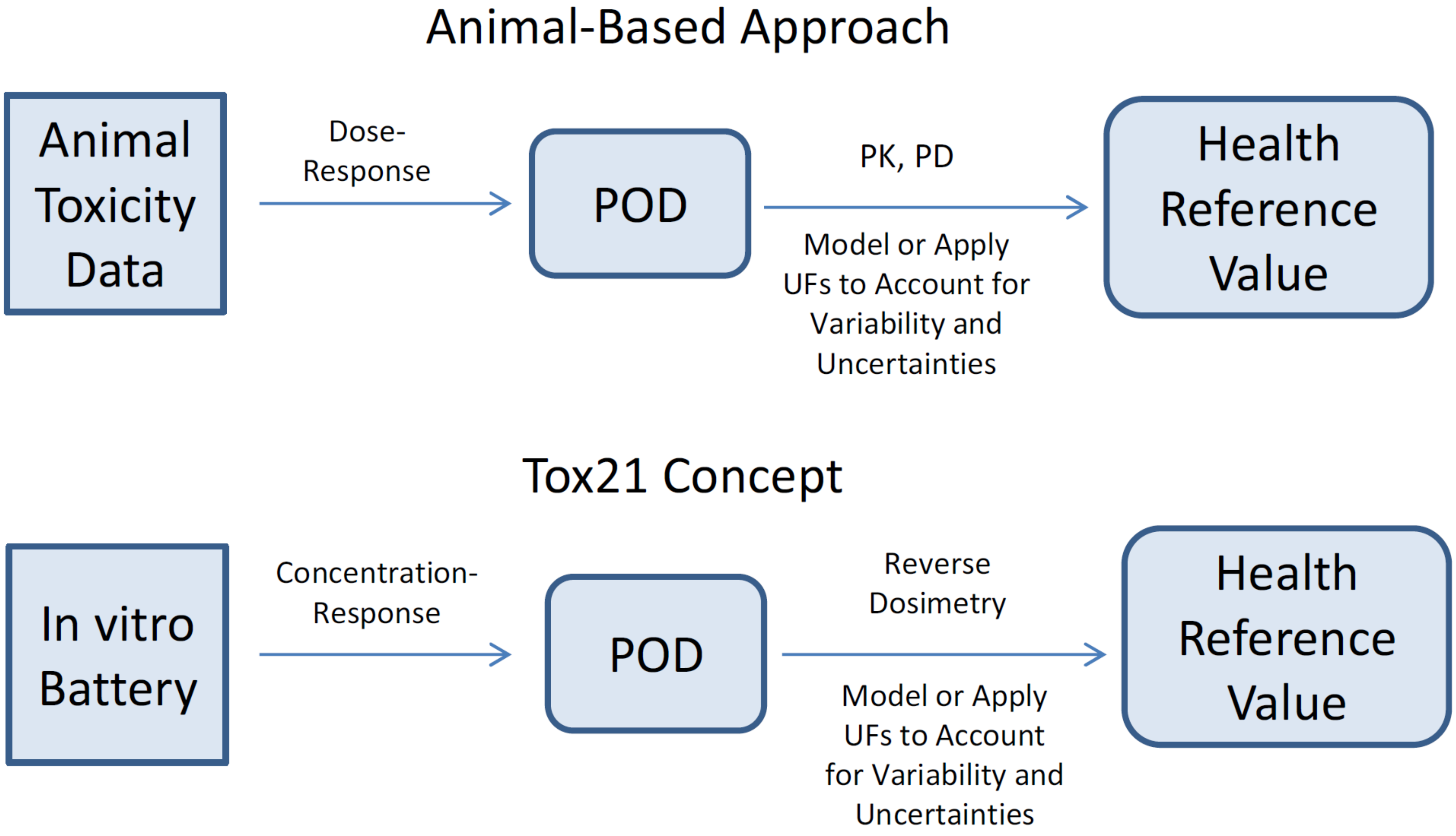
**"Site-specific" assessments:** Can involve selection of geographic sites or chemicals/mixtures at a contaminated site to evaluate.

**Assessment of new and complex chemistries:** Can involve assessment of green chemistry, new and complex substances, and unexpected environmental degradation products of chemicals in commerce.

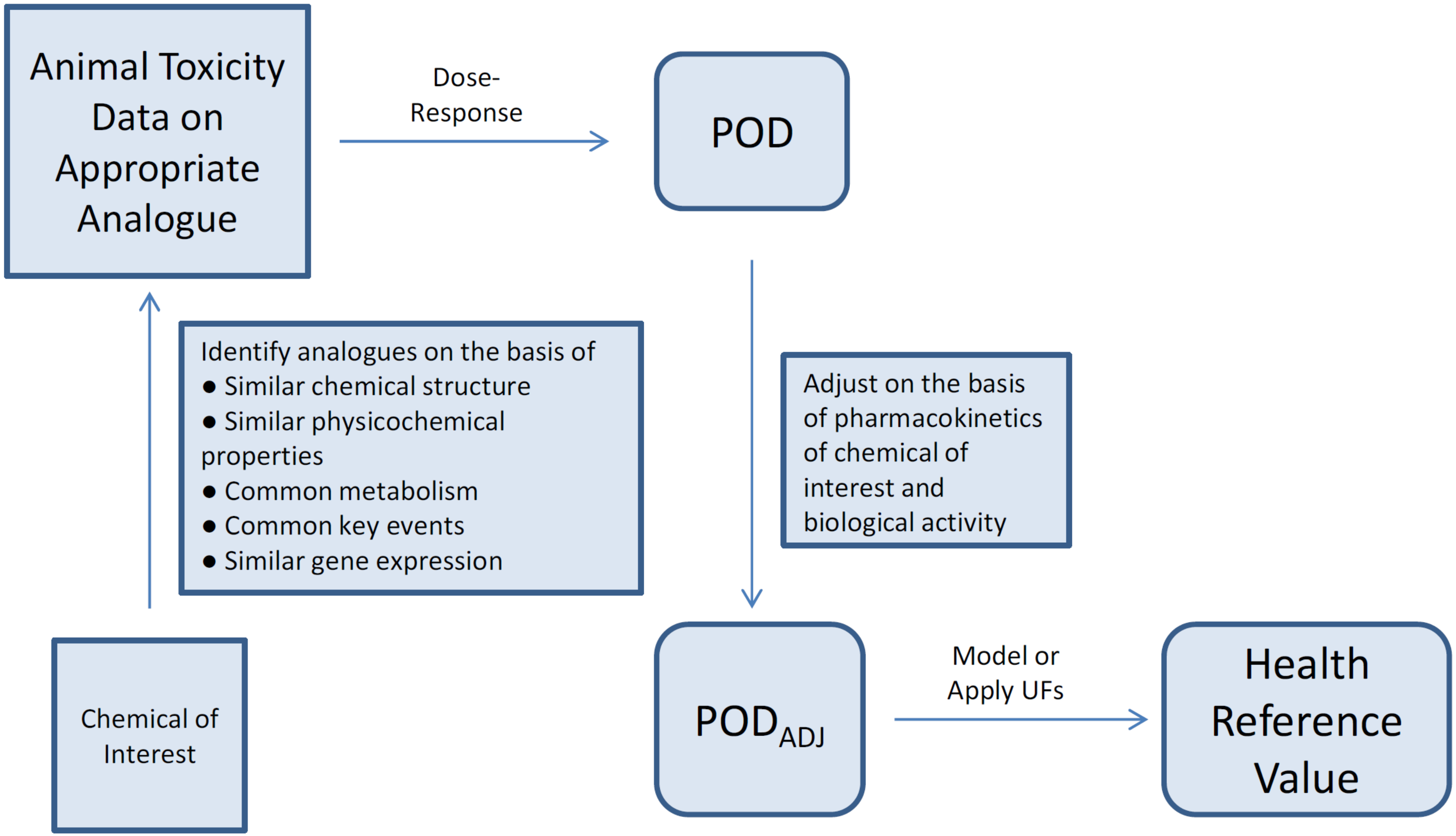
# Priority-setting



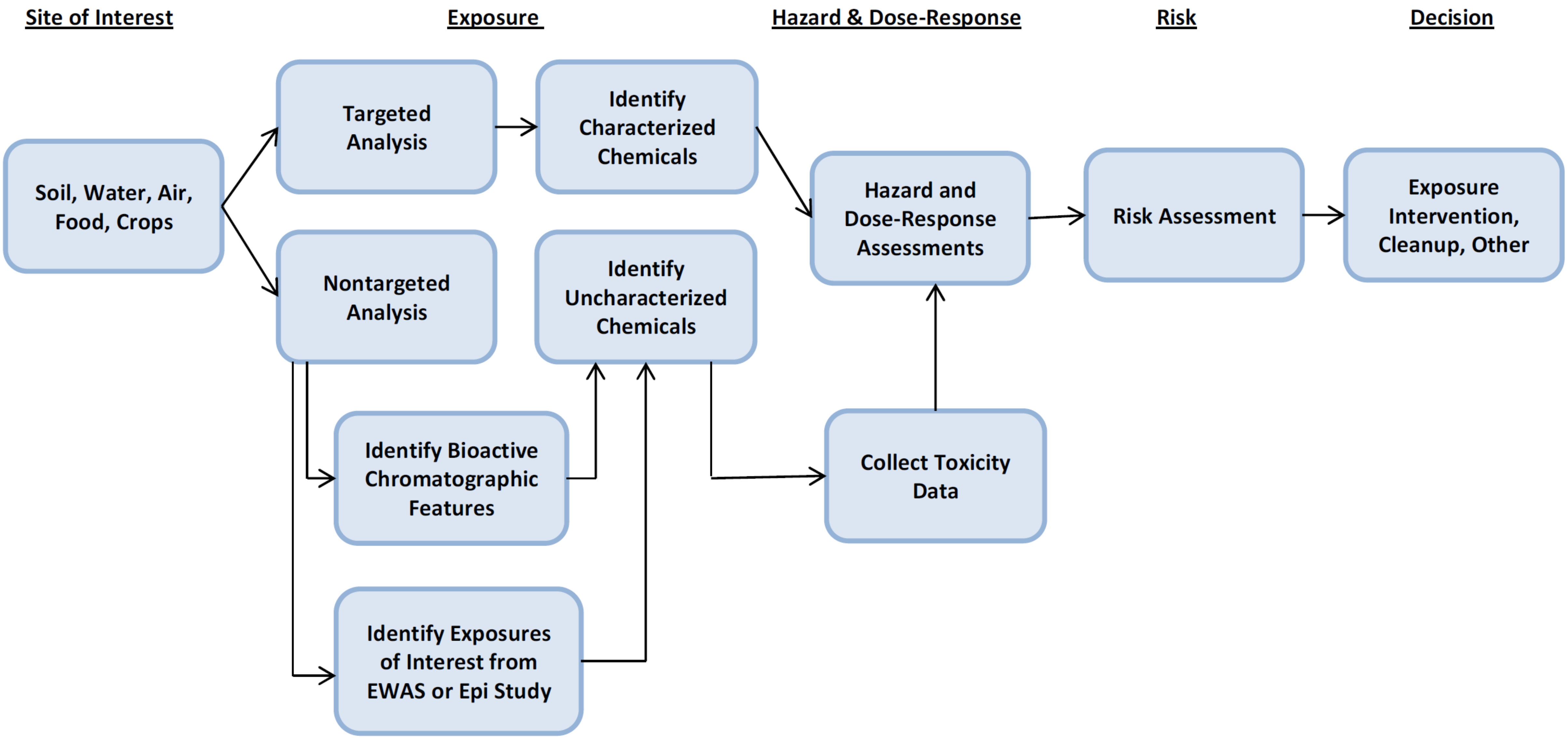
# Assessment of mono-constituent chemicals



# Assessment of mono-constituent chemicals



# “Site-specific” assessments



# The Future is Bright, Even Though…

- With the shift from observing apical responses to measuring molecular and pathway readouts there will be a greater role for mechanistic research.
- Bradford-Hill causal inference guidelines need to be modified for use with the new types of toxicology, exposure and epidemiology data.
- The data that are being generated today can be used to help to address many of the risk-related tasks that agencies face.
- Communicating the results of complex data analyses from the new types of toxicology, exposure and epidemiology studies is a major need.
- **Guided expert judgment should be used in the near term for integrating diverse data streams for drawing causal conclusions.**

## *Analogue Read-Across*

## Chemical-Biological Read-Across

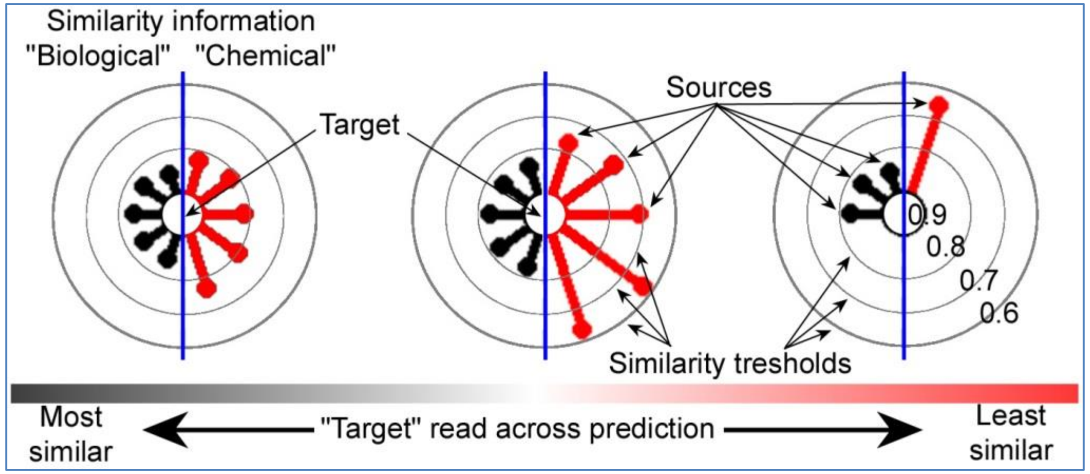
Chemical Research in Toxicology

Article

pubs.acs.org/crt

**Integrative Chemical–Biological Read-Across Approach for Chemical Hazard Classification**

Yen Low,[†,‡] Alexander Sedykh,[†] Denis Fourches,[†] Alexander Golbraikh,[†] Maurice Whelan,[‡] Ivan Rusyn,[*,‡] and Alexander Tropsha[*,†]




## *Category Read-Across*

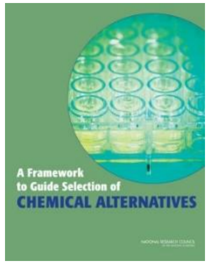
## Toxicology Priority Index (ToxPi)

BIOINFORMATICS APPLICATIONS NOTE Vol. 29 no. 3 2013, pages 402–403
doi:10.1093/bioinformatics/bts686

*Systems biology* Advance Access publication November 29, 2012

**ToxPi GUI: an interactive visualization tool for transparent integration of data from diverse sources of evidence**

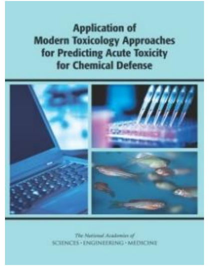
David M. Reif[1,*], Myroslav Sypa[2], Eric F. Lock[2], Fred A. Wright[3], Ander Wilson[1], Tommy Cathey[4], Richard R. Judson[1] and Ivan Rusyn[2]

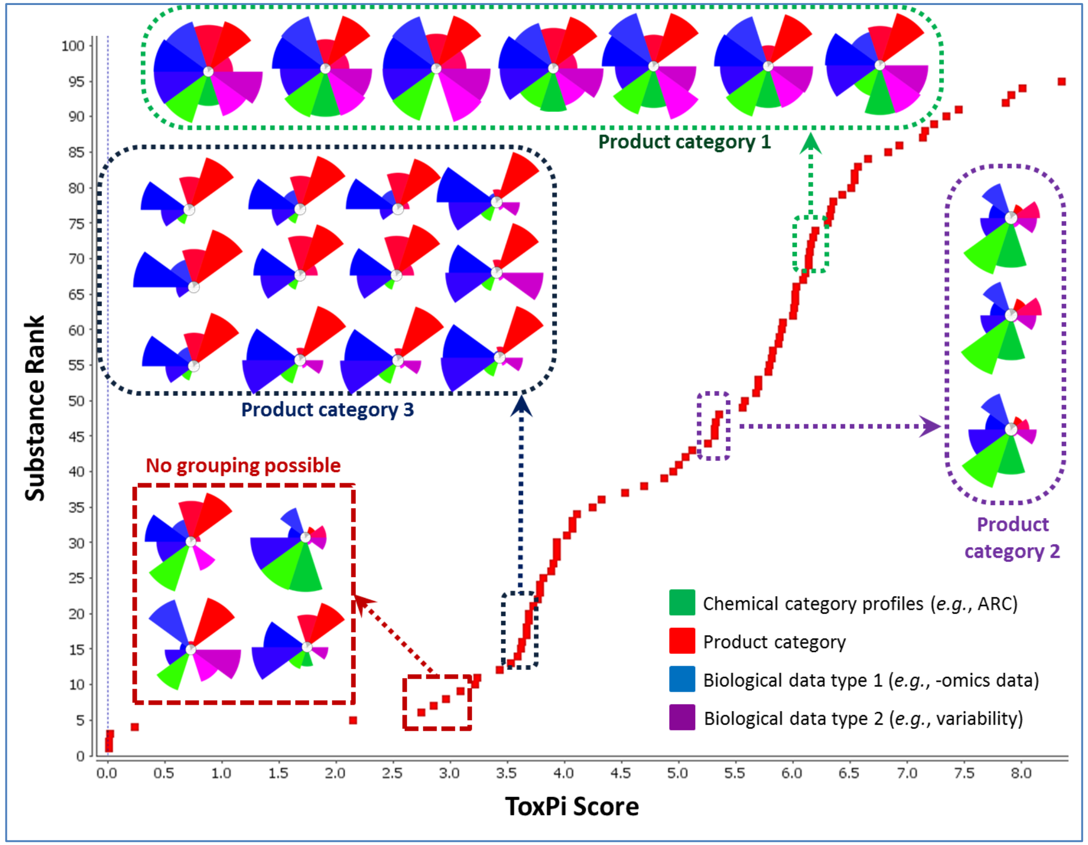



**Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data**

*David M. Reif,[1] Matthew T. Martin,[1] Shirlee W. Tan,[2] Keith A. Houck,[1] Richard S. Judson,[1] Ann M. Richard,[1] Thomas B. Knudsen,[1] David J. Dix,[1] and Robert J. Kavlock[1]*

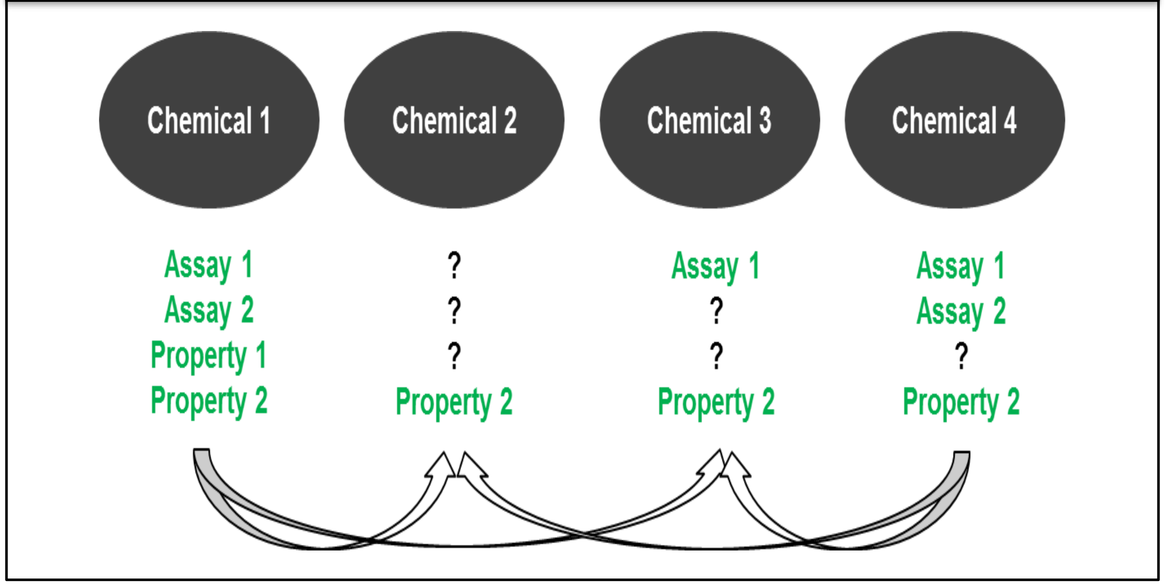
[1]National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA; [2]Office of Science Coordination and Policy, Office of Pollution Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, USA



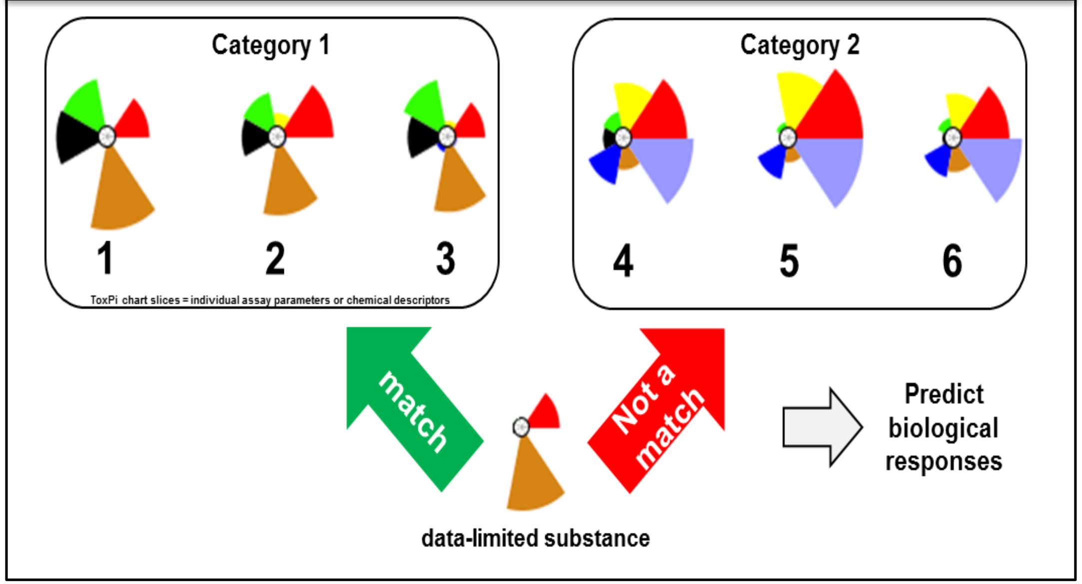



# Assessment of new and complex chemistries

## Traditional Read Across




## Toxicological data-based read-across




**Structural Categorization/Grouping**

**"Chemical" Read-Across**

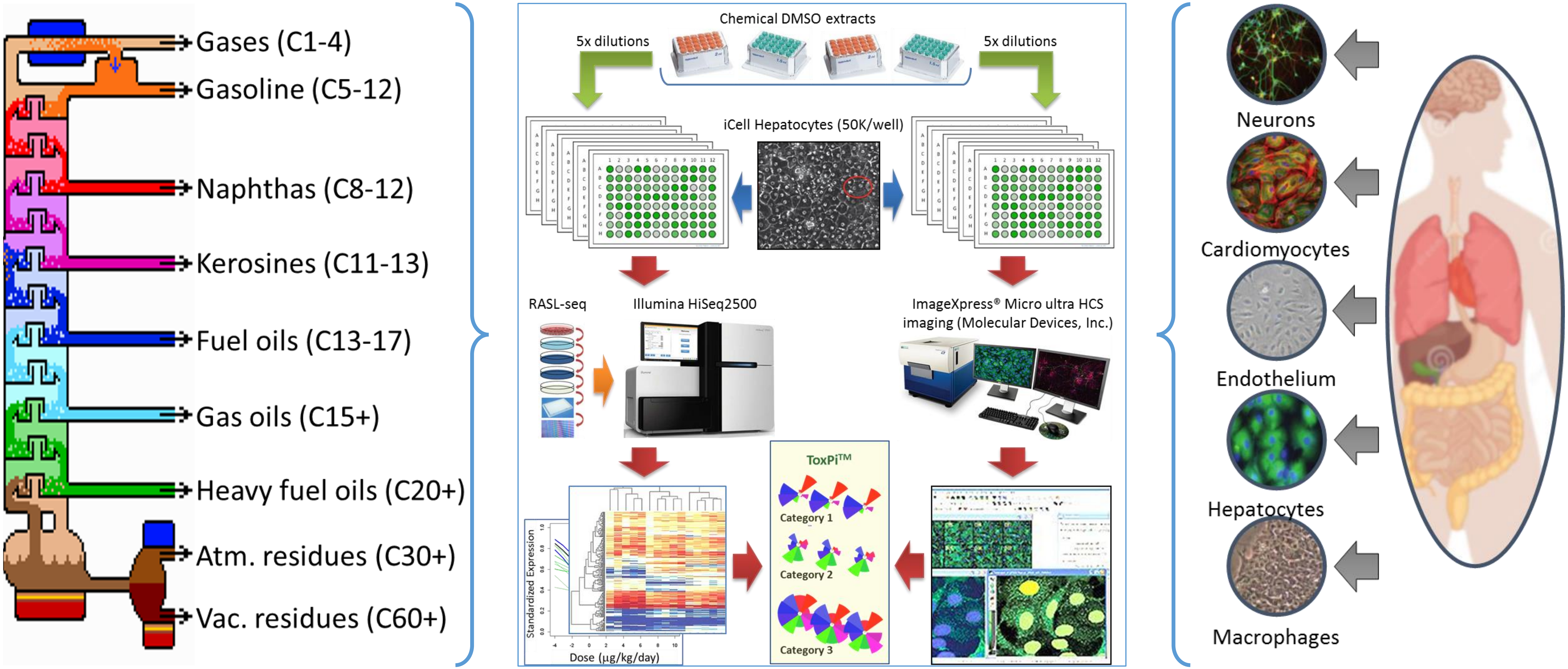
**Toxicological Categorization/Grouping**

**"Biological" Read Across**

**Complex Substances / UVCBs**

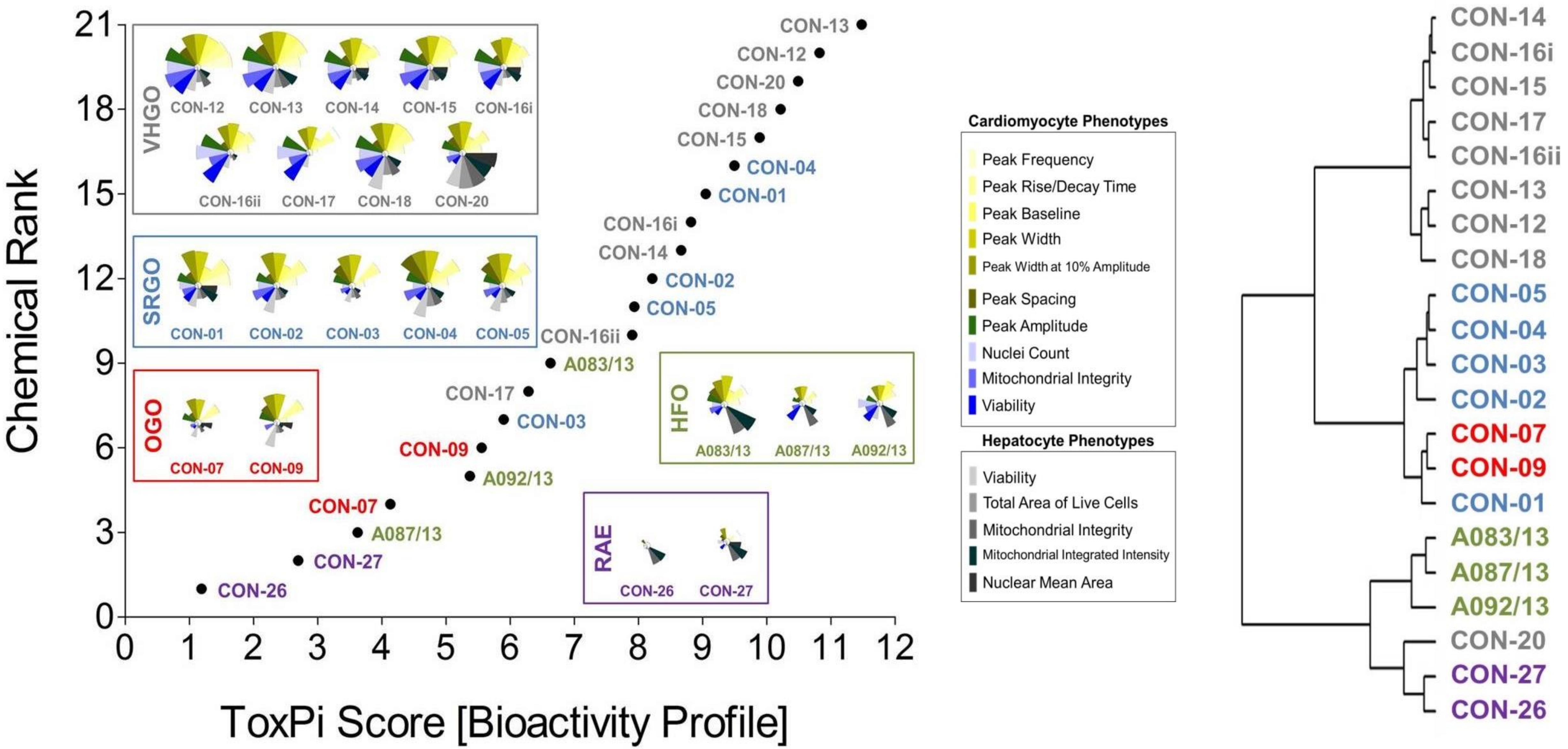
| | | |
|---|---|---|
| Not amenable to full chemical characterization | High Production Volume Chemicals | Batch-to-Batch Variability (same CAS) |

# Assessment of new and complex chemistries



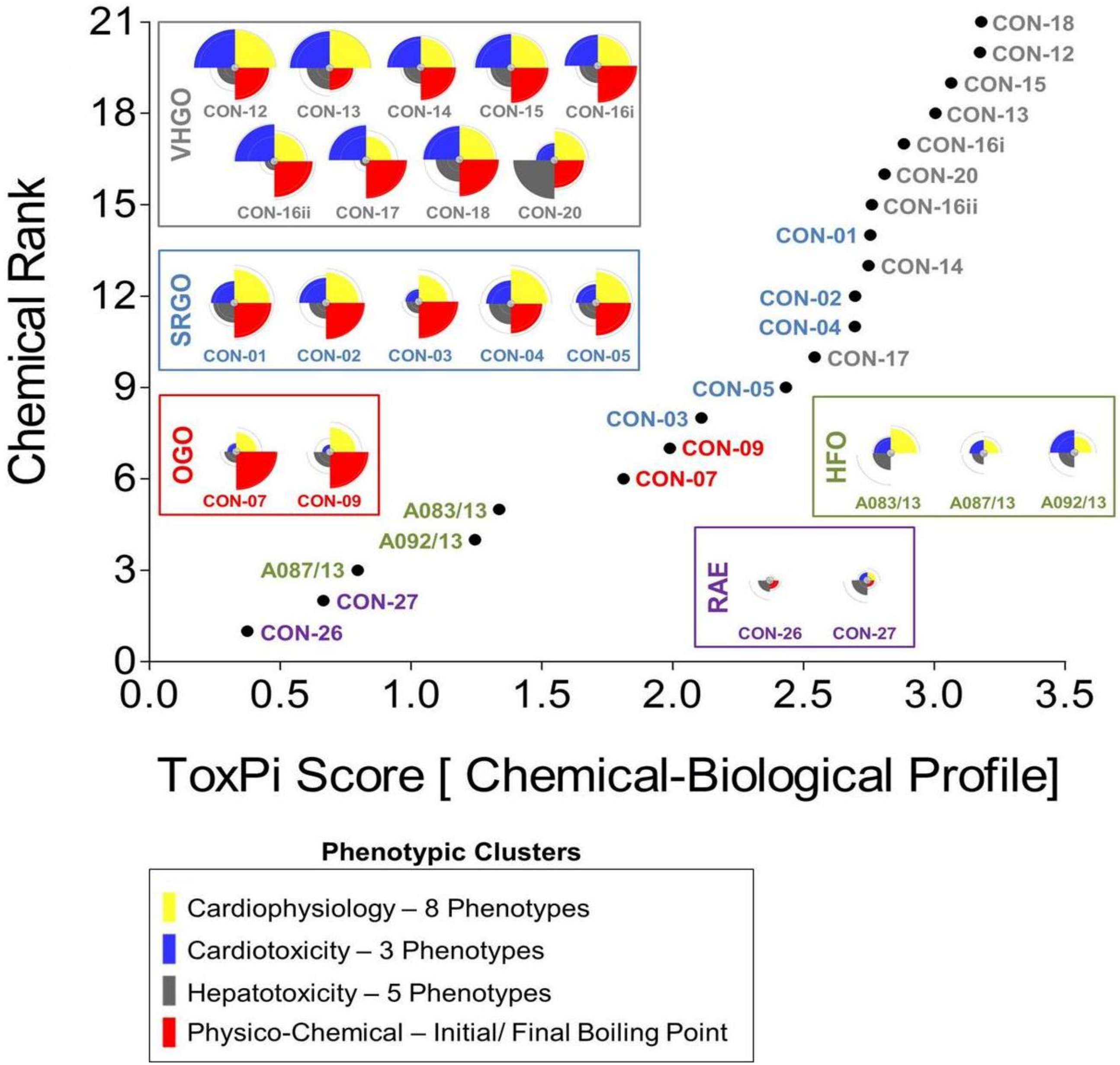

**Petroleum UVCBs** → **Bioactivity data-enabled read-across** ← ***in vitro* models**

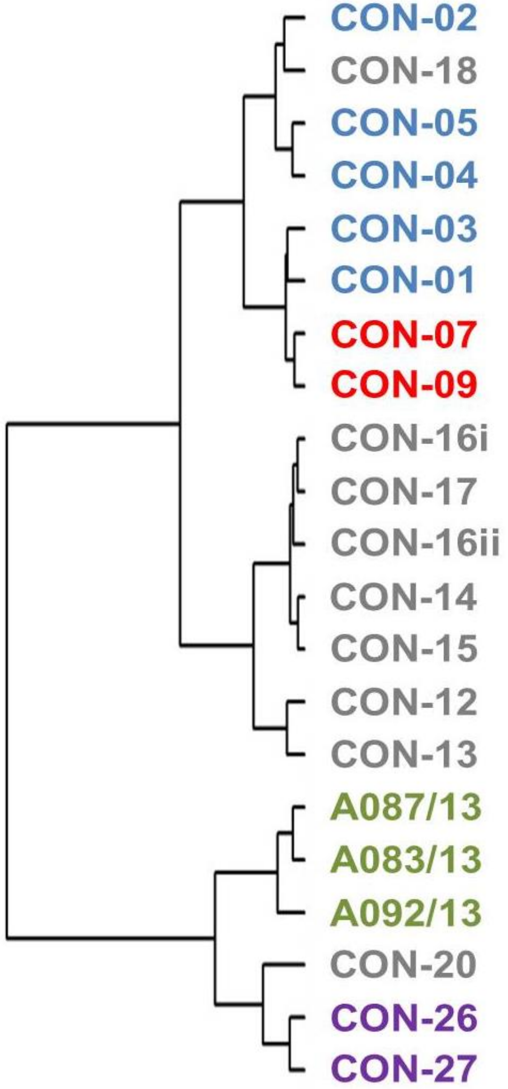
# Category Grouping of UVCBs: Bioactivity Profiles




Green Chem. 2016 Aug; 18(16):4407-4419

# Category Grouping of UVCBs: Bioactivity+P-Chem




Green Chem. 2016 Aug; 18(16):4407-4419

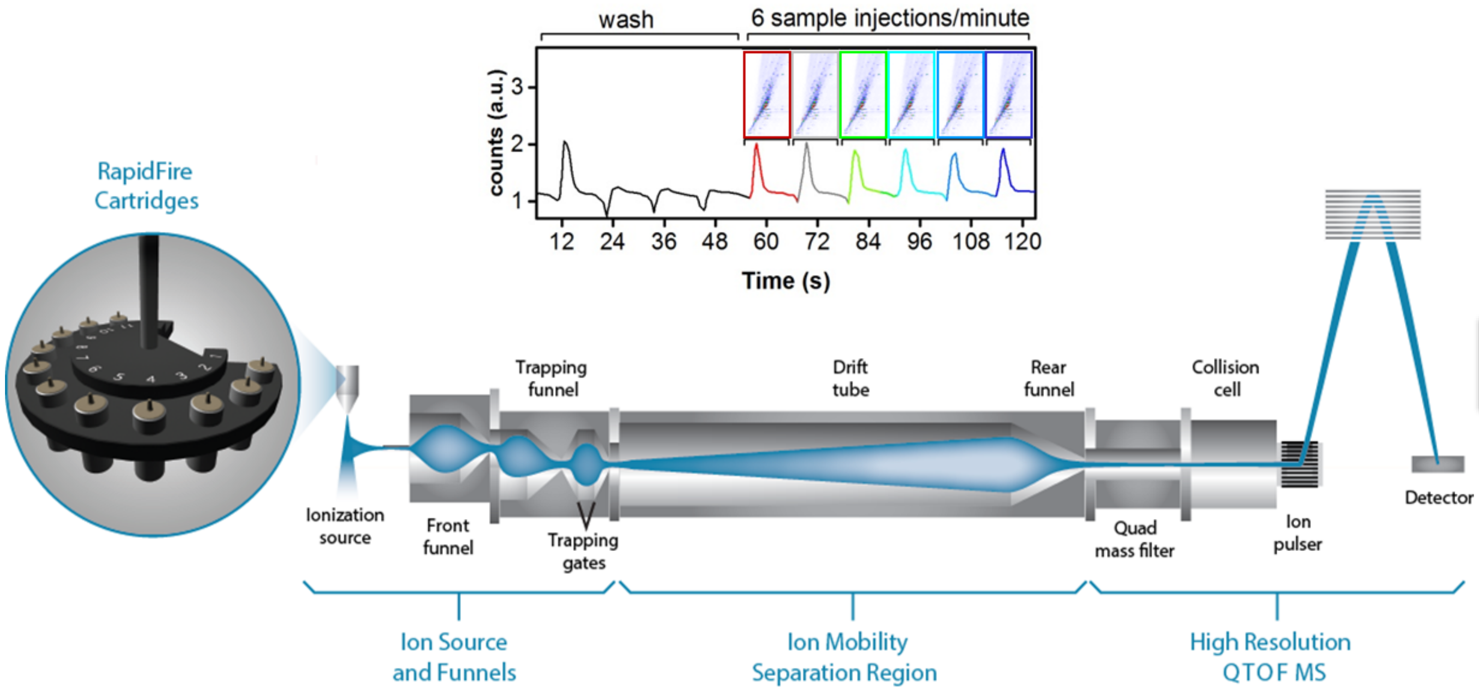
ECHA
http://echa.europa.eu

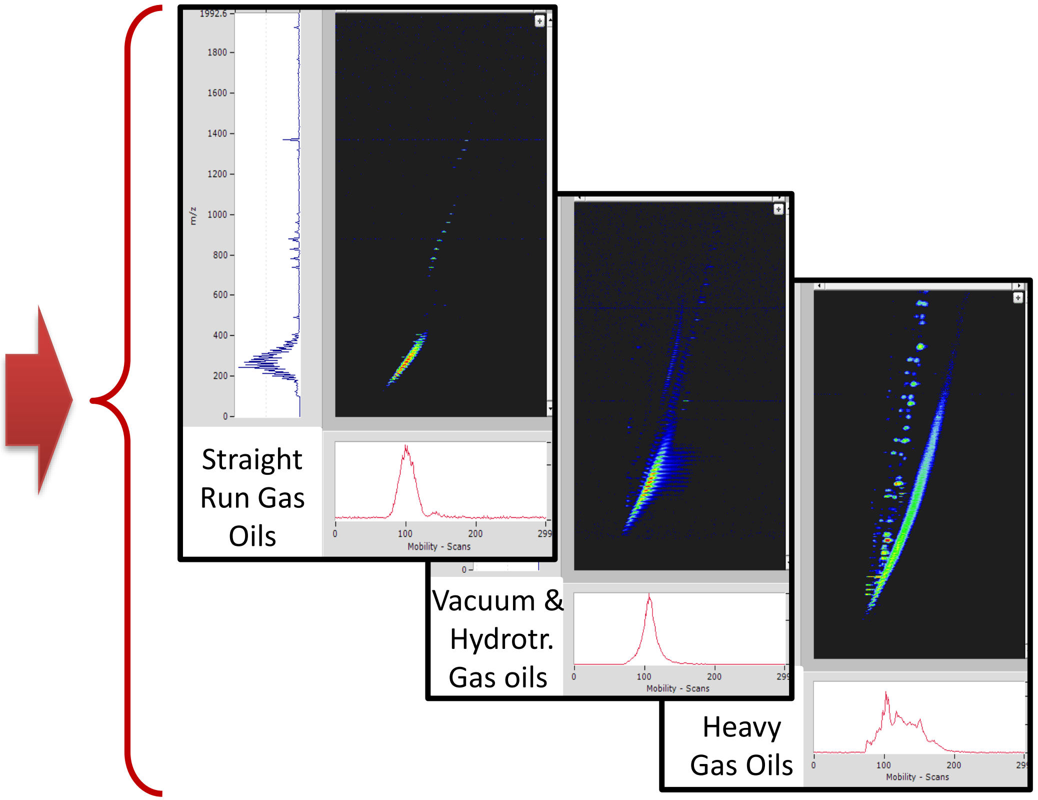
**Guidance for identification and naming of substances under REACH and CLP**

Feb 2014 (Version 1.3)
Section 4.3.1.3.

A chromatogram that can be used as a fingerprint shall be provided to characterise the composition of the substance. If applicable, also other valid constituent separation techniques might be used.

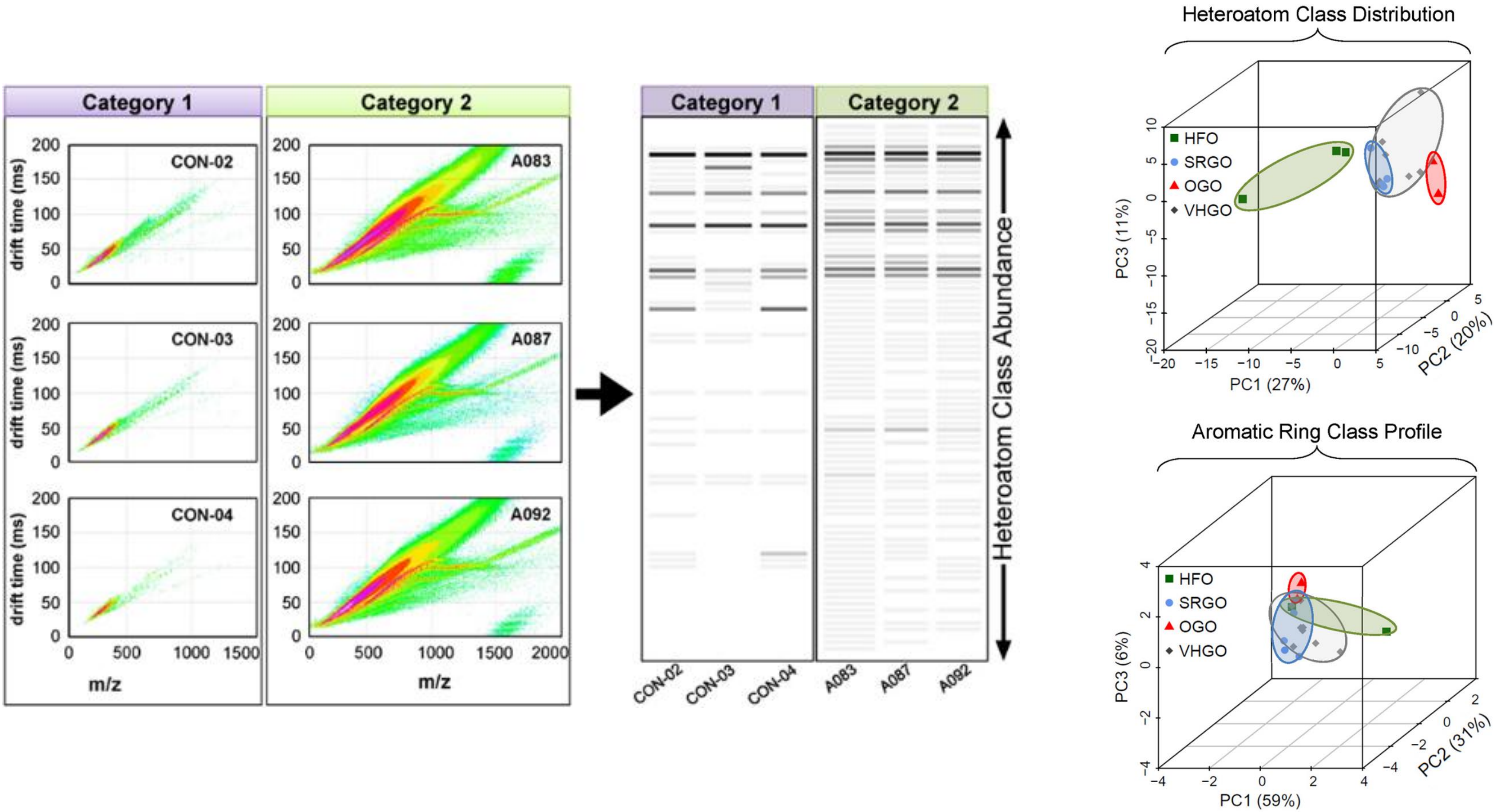
The identification parameters of REACH *Annex VI*, section 2 should be given. It is recognised that petroleum substances are manufactured to performance specifications rather than to compositional specifications. Therefore, characteristics like the name, carbon-chain length range, boiling point, viscosity, cut-off values and other physical properties are generally more helpful than compositional information in order to identify the petroleum substance as clearly as possible.



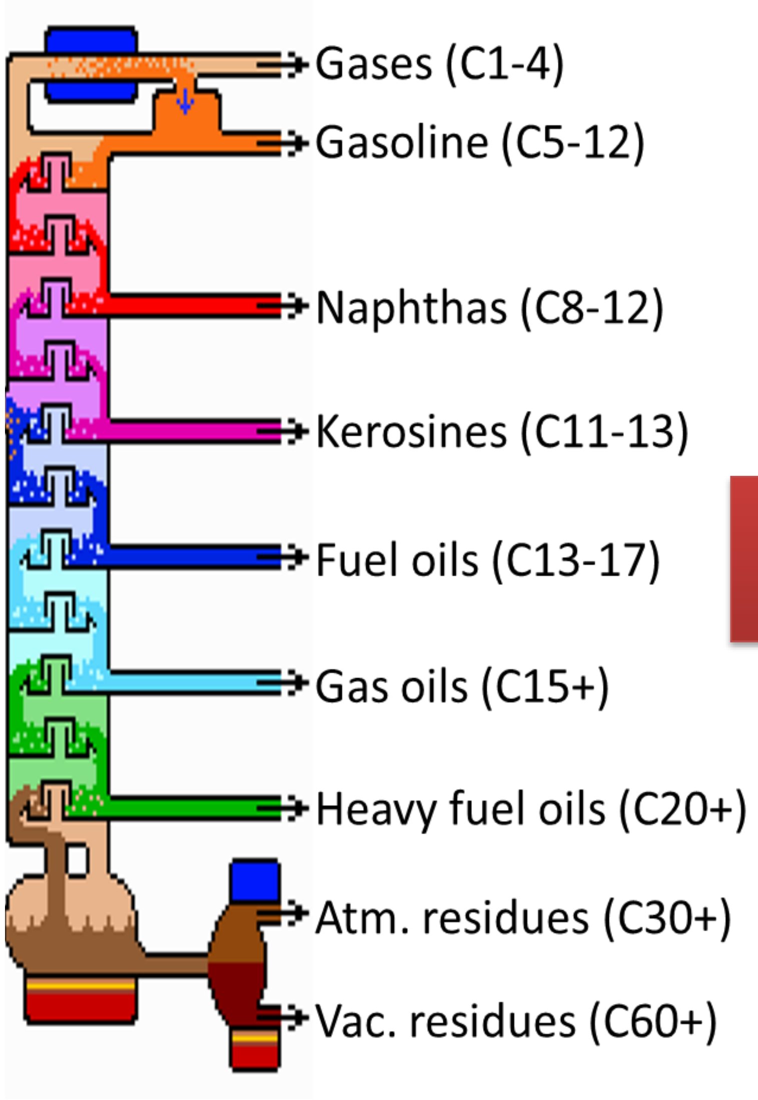



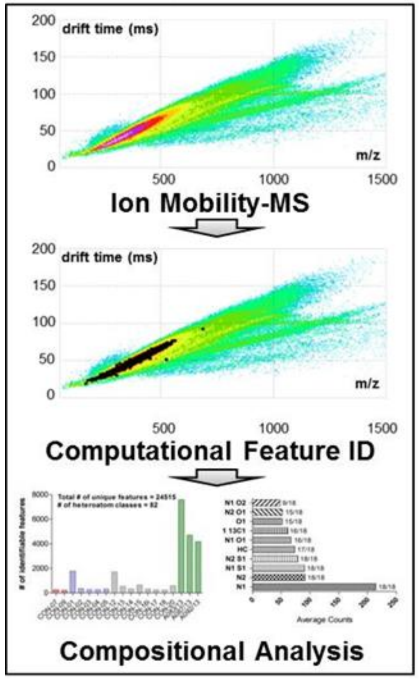

Anal Chem. 2016 Dec;88(24):12152-12160

# Category Grouping of UVCBs: High-Dimensional IM-MS

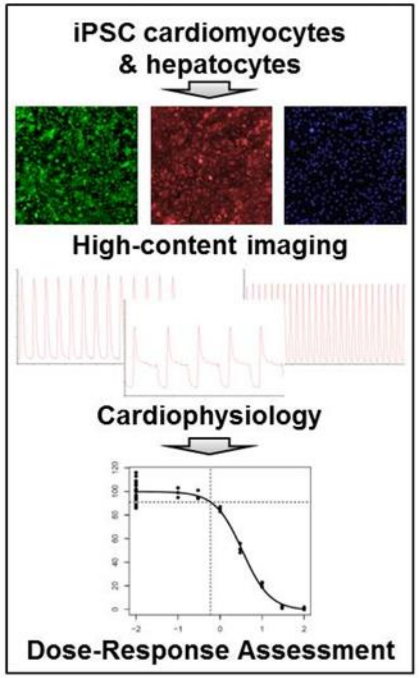


# Using New Methodologies for Better Understanding of the Health Impacts of Petroleum Substances

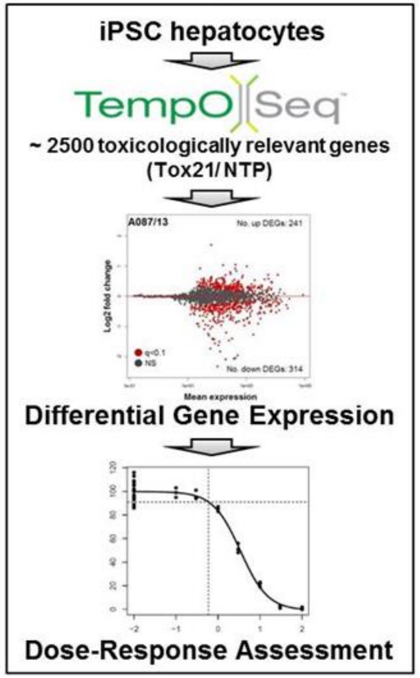



Novel analytical methods for compositional characterization




Novel cell-based assays for bioactivity profiling




Novel molecular techniques for mechanistic data

**Grouping and Read Across**